**Express Mail No.: EV654850700US**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | |
|---|---|
| Application of: RONALD J. PETTIS, *et al.* | Confirmation No.: 7814 |
| Serial No.: 09/606,909 | Art Unit: 3763 |
| Filed: June 29, 2000 | Examiner: Michael J. Hayes |
| For: INTRADERMAL DELIVERY OF SUBSTANCES | Attorney Docket No.: 11219-008-999 (500752-999007; P-4901) |

**DECLARATION OF DR. GERALD B. KASTING**
**UNDER 37 C.F.R. § 1.132**

**Mail Stop Amendment**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450
Sir:

I, DR. GERALD B. KASTING, do hereby declare and state:

1. I, Gerald B. Kasting, am a citizen of the United States, residing at 44 Mount Pleasant Avenue, Wyoming, Ohio.

2. I received a Ph.D. degree in physical chemistry in 1980 from Massachusetts Institute of Technology in Cambridge, MA under the supervision of Dr. Carl Garland. I was a research chemist at Procter & Gamble Company ("P&G"), from 1980 to 1993. In subsequent years, between 1993 and 1999, I continued as a Senior Scientist at P&G, directing research programs in the Health and Skin Care areas with a particular emphasis on topical and transdermal drug delivery and mathematical modeling of such delivery. From 1999 to the present, I have served as Associate Professor of Pharmaceutics and Cosmetic Science at the

College of Pharmacy in University of Cincinnati, Ohio, and from 2003 to the present, I have served with tenure in the same department.

3. As evidenced by my *curriculum vitae*, appendixed hereto (Exhibit A), I have been working in the field of transdermal and topical delivery of substances as of 1983. The focus of my research has been the analysis of structure-property relationships for delivery of agents through the skin and the development of predictive mathematical models for this phenomenon. Specifically, we have focused on the development of computational models for absorption of substances into and through the skin with the objective of developing better tools for prediction of topical drug delivery, transdermal drug delivery, and dermal exposure to noxious agents. My research group seeks to develop improved techniques for estimating the absorption rates of topically-applied therapeutic agents and for predicting local tissue concentrations and systemic loads resulting from dermal exposure to hazardous agents.

4. My academic background, technical experience and list of publications are set forth in my *curriculum vitae*, attached hereto as Exhibit A.

5. I am well versed in the biology and physical dynamics of both transdermal and topical delivery of agents, including drugs. I have served as a reviewer for a number of leading peer reviewed journals, including *J. Controlled Rel.*, *Pharm. Res.*, *Int. J. Pharm.*, *J. Invest. Dermatol.*, *Toxicol. Sci.*, *J. Pharm. Sci.*, and *J. Cosmet. Chem.*, and as an editorial board member for the latter two journals. I have published my work as well as various review articles in the field of drug delivery in numerous peer reviewed journals.

6. I have reviewed U.S. Patent Application Serial No. 09/606,909 (the "Pettis Application") which I understand was filed on June 29, 2000. I have also reviewed certain patents and publications that I have been informed were cited during the prosecution of the Pettis Application. More specifically, I have reviewed U.S. Patent Nos. 5,848,991 to Gross *et*

*al.* ("Gross"); 3,814,097 to Ganderton *et al.* ("Ganderton"); and Autret *et al.*, (1991, *Therapie*, 46:5-8; "Autret"). For purposes of this Declaration, I have been asked to evaluate two issues. First, I have been asked to review the Pettis Application (including its claims, *e.g.*, Claim 29) and comment on the teachings of the Pettis Application and what these teachings would provide to one skilled in the art as of June 2000. Specifically, I have been asked to evaluate whether, by June 2000, a skilled practitioner in the field of drug delivery would, using ordinary skill, be able to successfully deliver drugs with the improved pharmacokinetic profiles claimed following the teachings and guidelines set out in the Pettis Application. Second, I have been asked to comment on the disclosures of Gross, Ganderton and Autret and the distinguishing features, if any, of the teachings of the Pettis Application. I will address these two issues in turn below.

**Part I.** **Teachings of the Pettis Application**

7. By way of background, scientists in the art of drug delivery are concerned with obtaining systemic distribution of the drug to obtain the needed biological response for a particular therapeutic objective. Systemic distribution can be measured by monitoring plasma drug concentration to determine the pharmacokinetics of the drug -- that is, how the body acts on the drug. Typically, blood samples are taken periodically to measure the plasma concentration over time until the drug has cleared the system. This mode of monitoring was well known and established to those in the art of drug delivery as of the filing date of the Pettis Application -- that is, in June 2000. Practitioners in this art were prepared to routinely conduct pharmacokinetic studies in animal models to characterize the pharmacokinetic profile of a drug. (*See, e.g. The Merck Manual of Diagnosis and Therapy*, 1999, Seventeenth edition, Beers and Berkow, *ed.*, Merck Research Laboratories, Division of Merck & Co., Inc. Whitehouse Station, N.J. (pp. 2559-2567), attached hereto as Exhibit B).

8. To summarize, the Pettis Application describes a methodology for the delivery of drugs to the intradermal compartment of a subject's skin for systemic distribution, using insulin and PTH as an example. According to the Pettis Application, drugs can be delivered intradermally to achieve improved pharmacokinetic profiles when the following critical features are taken into account: (a) accurate positioning and placement of a needle of appropriate length so that its orifice is located within the intradermal compartment (*see,* specification at p. 4, *ll.* 3-28; p. 4 *l.* 29 to p. 5, *l.* 21); and (b) application of pressure in an amount sufficient to control the rate of delivery of the drug (*see,* specification at p. 5, *ll.* 22-28). The method is illustrated by the improved pharmacokinetic profiles achieved for the delivery of insulin and PTH by the intradermal route.

9. A scientist reading the Pettis Application would understand that its teachings are exemplified using insulin and PTH. There is no basis, scientific (or otherwise) to limit the teachings of the specification to insulin and PTH. A scientist armed with the Pettis Application and the technology known to him as of June 2000 would be able to apply the teachings of the invention to other drugs by taking into account the properties of the drug (*e.g.*, the drug's chemical composition, metabolism, and intended use). Moreover, given the compelling results presented in the Pettis Application for insulin, a large molecular weight molecule, a scientist attempting to apply the teachings of the Pettis application to other substances would be optimistic that following the instructions in the Pettis Application would present no impediment to the intradermal delivery of such substances.

10. The Pettis Application teaches that accurate positioning and placement of a needle of appropriate length, shape and structure is the first consideration for achieving intradermal delivery of a drug. The specification provides detailed disclosure regarding the length, shape, form and number of needles that are needed for intradermal delivery (*see,* specification at p. 4, *ll.* 3-28; p. 4 *l.* 29 to p. 5, *l.* 21). The Pettis Application teaches the importance of not only

the needle length but also the shape of the orifice, *e.g.*, exposed height and outlet depth. In the 'Detailed Description of the Invention", the Pettis Application describes the use of microneedles that have *both* a length sufficient to penetrate the intradermal space and an outlet depth within the intradermal space to allow the skin to seal around the needle to prevent effusion of the substance onto the surface of the skin due to backpressure (*see*, specification at p. 5, *ll.* 6-10).

11. The Pettis Application further provides guidance on how to address mechanisms that can be used to provide adequate pressures to control the rate of delivery of the drug so that the drug is consistently delivered to the intradermal compartment of the subject's skin. The Pettis Application clearly sets forth to a scientist reading the application that any of the devices commonly used to generate pressure in an amount sufficient to control the rate of delivery of any drug (*see*, specification at p. 7, *ll.* 25-25, listing for example, pumps, syringes, elastomeric membranes, osmotic pressure, and Belleville springs or washers) may be used in accordance with the invention. A scientist reading the Pettis Application would understand that controlling the application of the pressure is important to prevent the drug from effusing out of the skin which is expected as a result of pressure build up from injection of a substance into a small space.

12. In following the teachings of the Pettis Application, once a scientist has chosen a device having a needle with the appropriate length and shape placing the orifice within the intradermal compartment, the next step would be the application of pressure in an amount effective to control the rate of delivery of a drug for obtaining the desired pharmacokinetic profile. In order to determine the absolute value of the pressure for the delivery of the drug, a scientist would know and expect a certain amount of trial and error experimentation. The scientist would simply assay a series of pressures to arrive at the optimal pressure to achieve the desired pharmacokinetic profile for the drug of his choice. At the onset, a visual

inspection for leakage or excessive weal formation at the site of delivery will allow the scientist to choose a specified pressure as a starting pressure point for intradermal delivery (*see*, the Pettis Application at p. 5, *l.* 22 to p. 6, *l.* 14). The next series of pressures are then chosen in increments above and below the starting point pressure in order to determine the optimal pressure for delivery -- that is the optimal pressure for delivery of a drug for obtaining the desired pharmacokinetic profile. Once the pressure range is chosen, the experimental scheme may comprise the following steps: (1) delivering the drug at a pre-determined pressure within the empirically determined pressure range to the intradermal compartment; (2) taking periodic blood samples to measure the concentration of the drug in the blood until the drug has cleared the system (the number of time points depends on the metabolism of the drug); (3) plotting the blood concentration of the drug over time to obtain a pharmacokinetic profile; and (4) comparing the pharmacokinetic profile to that obtained from subcutaneous delivery of the same drug. If the desired pharmacokinetic profile is not achieved, steps 1-4 will simply be repeated at a different pressure setting. Once the optimal pressure is chosen for intradermal delivery of the drug of choice, the pharmacokinetic profile will be reproducible at that pressure, producing in effect a fingerprint of the drug.

13. Following these teachings of the Pettis Application, a scientist would know to choose a device having a needle so that its orifice is positioned within the intradermal compartment and apply pressure in an amount effective to control the rate of delivery of the drug so that the desired pharmacokinetic profile would be obtained--a pharmacokinetic profile with a higher $C_{max}$ and AUC as compared to delivery of the same drug to the subcutaneous compartment.

14. As I mentioned, such assay schemes requiring the monitoring of drug plasma concentration over a period of time are routinely done in the art of drug delivery to monitor doses of drugs to arrive at accurate dosing regimens for a particular therapeutic effect and

biological response. Thus, even though the amount of experimentation and the time required to carry out such experiments might appear daunting to the lay person, a practitioner in the art of drug delivery would expect it. In fact, when devising experiments in a pre-clinical setting scientists are often cognizant that extrapolation to a clinical setting would require further additional experimentation.

15. Thus, from my perspective, the technology described in the Pettis Application requires a certain amount of experimentation to determine optimal parameters of drug delivery. However, the nature of such experimentation invokes commonly known methodologies and the extent of such experimentation is simply not surprising and is in fact expected.

16. In sum, by June 2000, a skilled practitioner in the art of drug delivery could, using common methodologies known in the art, successfully deliver drugs into the intradermal compartment and achieve improved pharmacokinetic profiles, following the teachings and guidance of the Pettis Application. A scientist would take into account the critical features of the Pettis Application and choose a device having a needle so that its orifice is positioned within the intradermal compartment and apply pressure in an amount effective to control the rate of delivery of the drug so that the desired pharmacokinetic profile would be obtained. Since the scope of the applicability of the teachings of the Pettis Application is not limited to a particular drug, a scientist armed with the Pettis Application and the available technology as of June 2000, could adopt the teachings of the Pettis Application for intradermal delivery of any drug of choice.

**Part II.** **Relevant Art**

17. I understand that the Pettis Application has been rejected for lacking an inventive contribution over Autret, Ganderton and Gross, purportedly because the cited references disclose the teachings of the Pettis Application. I respectfully disagree and the reasons for my opinion follow.

18. The purported intradermal device and method described in Autret fail to deliver a substance to the intradermal compartment of the subject's skin which is the subject matter of the Pettis Application. In particular, the length and shape of the needle described by Autret is a Lebel single usage needle 4 mm in length with a diameter of 0.4 mm (*see*, Autret at p. 2 of the translation). A needle of such length is outside of the range of needle lengths prescribed by the Pettis Application. Additionally, Autret requires inserting the needle at an angle of approximately 60° from the surface of the subject's skin. Such placement of the needle would result in an angle of about 30° from the normal to the subject's skin, and carrying out basic trigonometric calculation would result in placing the tip of the needle about 3.5 mm deep in to the subject' skin--deeper than the depth taught in the Pettis Application. Thus, despite Autret's characterization of its mesotherapeutic method as "intradermal" the methods described do not result in delivering the substance to the intradermal space as defined in the Pettis Application. In fact, following the method described in Autret, the substance would be delivered non-specifically into the dermis and hypodermis--the fat layer of the skin. The mode of delivery taught in the Pettis Application is thus distinguishable from the Autret method, which results in selective and accurate delivering of the substance to the intradermal compartment of the subjects' skin.

19. Autret is distinguishable from the Pettis Application on other grounds. Autret does not describe the pharmacokinetic profile recited in the claims of the Pettis Application. The pharmacokinetic profile disclosed in Autret (*see*, Autret, Fig. 1) is not improved over

subcutaneous delivery--in fact, the profiles for the two routes of delivery are nearly identical. For example, Autret's pharmacokinetic profile does not exhibit both an increased $C_{max}$ and an increased AUC as required by the claims in the Pettis Application (*e.g.*, Claim 29). While this conclusion is readily apparent from visual inspection of the pharmacokinetic profile, Autret's own characterization of the data supports my position and analysis as well. In the Summary section of the publication, at p. 5, Autret states the following: "[n]either mean plasmatic levels at each plasmatic dosage nor mean areas under the curve....were significantly different" when Autret's method was compared to the subcutaneous route of administration. As summarized by Autret in the Discussion section, "[t]here is *no difference* in one and the same subject between the two routes of administration [intradermal and subcutaneous] as concerns...AUC...*Only* the Cmax is greater with the ID route." *See*, Autret at. p. 10 of the translation. Thus, with respect to pharmacokinetic profiles Autret and the Pettis Application are distinct.

20. Ganderton does not describe an intradermal delivery system which is the subject matter of the Pettis Application. In fact, Ganderton describes a multiple needle array technology, which has in fact been discredited since the late 1990s for failing to achieve a consistent and reproducible mode of drug delivery. The failure of the Ganderton based technology to provide an effective delivery is due, in part, to the inability of closely spaced needles to apply enough pressure to the surface of the skin, except for, at best, puncturing the outer layer of the skin, the stratum corneum. By way of analogy, Ganderton's system is similar to a bed of nails. If there were only one nail, the entire force created by the weight of the body would be distributed over the very small area presented by the tip of the one nail. In this case, the force per unit area, that is, the ratio of the force to the area, would be very great (because the area is small) and would likely result in piercing of the skin. However, when a 'bed' of nails is used, the same force produced by the weight of the body is distributed over

perhaps hundreds of nails. Therefore, the force applied to any one nail is correspondingly reduced, with the result that the force per unit area at the tip of any one nail will be well below the level required to pierce the skin. Since this applies to all the nails in the bed, no nail then penetrates the skin. Similarly, in Ganderton's system since there are multiple fibers the force applied to any one fiber is reduced, resulting in a low force per unit area and at best a puncturing of the outer skin surface, without achieving penetration of any of the fibers into deeper layers of the skin, much less the intradermal space. The multiple fiber pad of Ganderton thus is distinguishable from the intradermal delivery system of the Pettis Application because at best it achieves topical delivery through a punctured stratum corneum.

21. Gross' purported intradermal delivery device is distinct from the intradermal delivery system taught in the Pettis Application. A careful reading of Gross indicates that while there might be some overlap in terms of needle length with the Pettis Application (*see*, Gross at col. 4, *ll.* 10-13) the reference as a whole fails to teach how to specifically deliver a substance into the intradermal compartment as taught in the Pettis Application. Critical features of the Pettis invention are simply absent from Gross. Unlike Gross, the Pettis Application teaches the importance of not only the needle length but also proper positioning of the orifice of the needle into the intradermal compartment of the subject's skin. There is absolutely no disclosure in Gross concerning the height and depth of the needle outlet or the criticality of its placement within the intradermal compartment. Gross does not describe insertion of a needle so that both its outlet depth and exposed height of the outlet (*i.e.*, orifice) are located within the intradermal compartment of the subject's skin. This feature however is a requirement specified in Claim 29 of the Pettis Application and described in the Pettis Application.

22. In fact, even Gross recognizes that its alleged intradermal device does not specifically target the intradermal space. As described in Gross, the Gross devices are designed to administer the drug in a non-selective fashion "below the epidermis, *i.e.*, to the interface

between the epidermis and the dermis *or* to the interior of the dermis *or* subcutaneously" (*see*, Gross at col. 3, *ll.* 39-42; emphasis added). In other words, the devices lack the specificity mandated by those in the Pettis Application--which specifically and selectively deposit a drug into the intradermal compartment of the subject's skin. The delivery systems disclosed in Gross, even though named an intradermal device are by no means specifically targeting the intradermal space. Rather, by Gross' own admission its devices are designed to target various compartments of the skin--each compartment is treated in an equal handed manner. There is thus no disclosure in Gross on how to deliver specifically to one skin compartment to the exclusion of others.

23. The failure of Gross' devices to deliver a substance selectively into the intradermal compartment is, in part, explained by its lack of recognition of proper positioning of the orifice of the needle within the intradermal compartment. If the orifice of the needle (height and depth) is not located within the intradermal space, the application of pressure will not result in ID delivery in accordance with the Pettis Application -- placement of the outlet height above the ID compartment would result in leakage of the injected substance up and out of the injection site; while placement of the outlet depth below the intradermal compartment would result in delivery the subcutaneous compartment.

24. Gross also fails to appreciate the requirement for applying pressure in an amount sufficient to control the rate of delivery of the substance. Gross does not appreciate the shortcomings and limitations associated with gas-pressure driven devices which are prone to deviations in delivery rate as described in the Pettis Application. In fact, Gross treats gas pressure driven devices in the same manner as other pressure generating means. Gross thus provides no teaching of the criticality of the use of mechanical based systems for achieving reproducible and consistent rates of delivery essential for the specificity required for selective ID targeting.

25. Finally, Gross does not describe, measure or evaluate the systemic distribution or pharmacokinetic profile of any substance. More specifically, Gross does not disclose the pharmacokinetic profile required by the claims in the Pettis Application (*e.g.*, Claim 29), *i.e.*, a PK profile with a higher maximum plasma concentration and a higher bioavailability as compared to those obtained from SC delivery. In fact, a careful reading of Gross indicates that Gross does not measure or report plasma concentrations of any drug (*see*, Gross, Figs. 12 and 13).

26. In sum, Gross' failure to disclose the criticality of positioning of the orifice of the needle within the intradermal compartment and application of pressure in an amount sufficient to control the delivery rate of the substance precludes it from selectively targeting a substance to the intradermal compartment and thus achieving the desired PK profile specified in the Pettis claims. In other words, there is simply no guarantee following Gross' disclosure that one would necessarily target the substance to the intradermal compartment--it may happen, it may not.

27. I declare further that all statements made in this Declaration of my own knowledge are true, and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and that like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 19 of the United States code and that such willful false statements may jeopardize the validity of this application and any patent issuing thereon.

Gerald B. Kasting

Dated: October 6, 2005

GERALD B. KASTING